REMARKS

The Office Action dated May 8, 2008 has been carefully considered. Claims 1, 36 and 40 have been amended. Claims 17-23, 32-34 and 45-59 have been canceled. Claims 1-16, 24-31, and 35-44 are in this application.

Claims 17-23 and 45-59 drawn to an unelected invention have been canceled. Support for the amendment to claims 1, 36 and 40 is found through the specification and in particular on page 12, line 3 to page 13, line 10 and Examples 1 and 2. No new matter has been entered.

The specification was objected to for the use of the trademark EUDRAGIT. Applicants have amended the specification as requested by the Examiner.

Claims 1-16 and 24-44 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-16 and 25-51 of copending Application No. 10/315,801. Applicants note that this is a provisional rejection which does not prevent the claims of this application from issuing unless claims issue first in the copending application.

Since the claims of both applications are not yet finalized and may be substantially amended, Applicants is unable to respond to whether the instant claims are unpatentable over the claims of the copending application. However, if the double patenting rejection is still outstanding when the instant application is in condition for allowance, Applicants will file a Terminal Disclaimer at that time, if still required by the Patent Office.

Claims 1 -16 and 24-42 were rejected under 35 U.S.C. § 103 as unpatentable over U.S. Patent No. 4,851,231 to Urquhart et al. in view of U.S. Patent No. 5,718,919 to Ruddy et al. and U.S. Patent No. 6,675,995 to Roy et al.

Urquhart et al. teach a tablet comprising particles having 100 to 2000 microns in the form of a reservoir system of tiny reservoirs. The reservoir system comprises a wall of a rate controlling material surrounding the beneficial drug. The tablet containing tiny reservoirs is formed by spraying a wall material on a powdered drug to surround each drug core. Various thicknesses of the wall forming materials can be used for providing additional controlled release.

In contrast, the present claims comprise a pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix into a solid nano-sphere or in both the solid nano-sphere

and a micro-sphere. The matrix system provides release of the pharmaceutical active agent continuously from the solid nano-spheres for an extended period of time. As shown below in Fig. A, in a matrix system, the active is dispersed in a matrix and in a reservoir system the active is surrounded by a rate controlling membrane. Accordingly, a matrix system can provide prolonged release of an active agent from the matrix, whereas in the reservoir system, all the active will be released as soon as the coating or membrane is cracked. Thus, the release kinetics are very different between the matrix system of the present invention and the reservoir system of Urquhart et al.

Applicants submit that Urquhart et al. disclose a wall which acts as a barrier toward the active agent. In contrast, in the present invention, the nanoparticles are devoid of further coating, accordingly, there is no wall surrounding the nanoparticles to act as a barrier to the active and the active agent is released from the solid hydrophobic nanosphere as the agent diffuses from the hydrophobic matrix. Accordingly, the present invention relates to nanoparticles which are devoid of a coating and in particular a barrier coating to an active. Further, Urquhart et al. do not disclose the long lasting controlled release of the present invention.

Ruddy et al. disclose nanoparticles of a therapeutic agent. The nanoparticles have a surface modifier absorbed on the surface. In contrast to the invention defined by the present claims, Ruddy et al. do not teach or suggest a first pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix forming the core of a plurality of solid nano-spheres or incorporated into both the hydrophobic matrix of the plurality of solid nano-spheres by dispersion and the matrix material of the micro-sphere and do not cure the deficiencies of Urquhart et al. noted above. The Examiner stated that it would be prima facie obvious at the time of the invention to make the reservoirs of Urquhart et al. smaller, according to the teachings of Ruddy et al., it would follow that the matrix which encloses these particles would also be made smaller to retain the proportions taught in Urquhart et al., motivated by the advantages taught by Ruddy et al. However, Urquhart et al. do not provide enabling disclosure to one of ordinary skill on how to make the reservoirs smaller. If one depends on Ruddy et al. for enabling teaching, then one would form smaller reservoirs by grinding down the preformed reservoirs. (See Ruddy et al. at Col. 5, line 30 et seq.). This would grind away the walls surrounding the

drug and make the reservoirs inoperable for their intended purpose. The alternative method of forming smaller particles taught by Ruddy et al. involves forming a dispersion. This method does not provide for the *solid* nanospheres required in the claims. Thus the Examiner has not shown that one of ordinary skill in the art was capable of transforming the reservoirs of Urquhart et al. into solid nanospheres of the size of the invention at the time the invention was made. Accordingly, the invention defined by the present claims is not obvious in view of Urquhart et al. in combination with Ruddy et al.

Roy et al. teach oral delivery of nucleic acid vaccines using DNA nanosphere. The nanospheres are prepared by a solution of gelatin and chitosan. In contrast to the invention defined by the present claims, Roy et al. do not teach or suggest a first pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix forming the core of a plurality of solid nano-spheres or incorporated into both the hydrophobic matrix of the plurality of solid nano-spheres by dispersion and the matrix material of the micro-sphere and do not cure the deficiencies of Urquhart et al. noted above. Accordingly, the invention defined by the present claims is not obvious in view of Urquhart et al. in combination with Roy et al.

With regard to claim 2, none of the references teach or suggest that first active agent is incorporated in the solid nano-spheres and further comprising a second active agent encapsulated in the pH sensitive or salt sensitive matrix material wherein the pH sensitive or salt sensitive matrix material releases the second active agent upon contact with a solution having a predetermined pH or predetermined salt concentration.

Claims 40-44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,851,231 to Urquhart et al. in view of U.S. Patent No. 5,718,919 to Ruddy et al. and U.S. Patent No. 5,543,158 to Gref et al. Applicants rebut the rejections with traverse.

The failures of Urquhart et al. to teach all the limitations of the claims, as discussed above, apply to the rejections under 35 U.S.C. § 103, as well, and cause the failure to present a prima facie showing of obviousness. In addition, the following further failure of the grounds for the rejections is addressed.

The Examiner stated it would have been obvious to attach antibodies to the nanospheres of Urquhart et al. according to Gref et al. However, this would not provide the invention of

claim 40. Urquhart et al. do not teach that the reservoirs contain poly(alkylene glycol) moieties on the surface yet Gref et al. requires such poly(alkylene glycol) moieties in order to attach the antibodies (Abstract and Col. 2, lines 30-47 of '158). Further, Urquhart et al. requires that the drug is surrounded by walls and that the walls meet certain structural requirements in order that they be permeable or subject to degrading when released from the surrounding matrix (Col. 6, line 20 to Col. 7). One of ordinary skill would have had no expectation of success that the walls would function as intended Urquhart et al., if they were reconstituted to include poly(alkylene glycol). Thus, the combination of Urquhart et al. and Gref et al. do not teach how to attach antibodies to the surface of the reservoirs of Urquhart et al. and do not provide the invention of claim 40.

In view of the foregoing, Applicants submit that all pending claims are in condition for allowance and request that all claims be allowed. The Examiner is invited to contact the undersigned should she believe that this would expedite prosecution of this application. It is believed that no fee is required. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2165.

Respectfully submitted,

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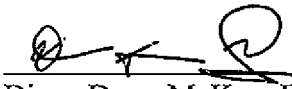

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Design of Controlled Release Systems

The transport of an active molecule through homogenous, nonporous materials occurs by a process of dissolution of the permeating molecules in the polymer.

Matrix Systems

The active is dissolved or dispersed in a matrix

Transient Diffusion

$$(\partial c/\partial t) = -D(\partial^2 c/\partial x^2)$$

Reservoir Systems

The active is surrounded by a rate controlling membrane)

Steady State Diffusion

$$J = -D(\partial c/\partial x)$$

Fig. A